REMARKS

The Present Invention

The present invention relates generally to immunological adjuvants for use in increasing efficiency of vaccines and in particular to improved oil-in-water emulsions.

The Pending Claims

Claims 1-35, directed to improved adjuvant formulations suitable for stimulating immune responses to molecular antigens in large mammals, are pending in this application and are the subject of a restriction requirement.

The Restriction Requirement

The Examiner has required restriction to one of the following groups of claims under 35 USC 121:

I. Claims 1-9 and 29-30, drawn to an adjuvant composition comprising an oil and an emulsifying agent and a method of stimulating an immune response using the composition of Claims 1-9 as an antigen.

II. Claims 10-27 and 31-35, drawn to the composition of Group I additionally requiring an immunostimulating agent and a muramyl peptide optionally attached to a phospholipid and to a method of using such composition for immunostimulation.

III. Claim 28, drawn to a vaccine.

Applicant affirms the provisional election with traverse to prosecute the invention of Group I (Claims 1-9 and 29-30) made during a telephone conversation between the Examiner and Applicant's representative on October 26, 1990.

By way of traversing the restriction requirement, Applicant points out that Claims 1 and 29 are generic claims which do not require an immunostimulating agent, and Claims 10-27, and 31-35 are not specifically drawn to such agents and, therefore, do not belong in Group II. Moreover, since all claims directed to muramyl peptides are dependent on generic claims such as Claims 1 and 29, such claims should be patentable if elected Claims 1 and 29 are patentable. (See MPEP §803 relating to a reasonable number of patentably distinct species which can be included in an allowable generic claim.)

The invention of Claim 28 is not separate and distinct from the inventions of Groups I and II were the vaccine contemplated in Claim 28 requires specific manufacture using the compositions and methods of Groups I and II.

For these reasons, Applicant respectfully requests that the restriction requirement be reconsidered and withdrawn.

The comments below respond to the Examiner's concerns based upon examination of Claims 1-9, 29 and 30 on their merits.

Section 112, First Paragraph

The Examiner's objection to the specification and rejection of Claims 1-9 and 29-30 under 35 U.S.C. §112, first paragraph are overcome, in part, by the above amendments to the specification and the claims, and otherwise traversed.

Applicant describes the phrase "a protective antigen" in the specification on page 25, lines 15-23, as an antigen that causes a host animal to produce a specific and immunological response which imparts protection to the host from subsequent exposure to the antigen. However, to improve the clarity of the claim, the term "protective" has been removed from Claim 29.

With regard to the proportion of ingredients in the present composition, the terminology on page 16, second paragraph generally discusses effecting reduction in oil

droplet size by changing the ratio of surfactant to oil. Especially preferred ratios of surfactant in the adjuvant formulation are set forth in the claims as originally filed (see original Claim 9) and constitute part of the complete disclosure. Thus, amendment of the specification to include the lower range value of surfactant as given in the claims does not introduce new matter. The Examiner is respectfully requested to enter this amendment to provide for conformity in the disclosure and overcome this rejection.

Section 102(b) or 103

Applicant respectfully traversed the rejection of Claims 1-9 and 29-30 under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103 as obvious over EPO 315153.

Allison et al. (EPO 315153) teaches an adjuvant composition and a method of using the same where the diameter of the oil particles is less than 800nm if a polyoxypropylene-polyoxyethylene block polymer is present. Thus, Allison's formulation requires the presence of block polymer, compounds which are specifically excluded in the present claims. Moreover, Applicant notes that Allison was published on May 10, 1989, only two weeks prior to the priority application filing date for the instant case. Therefore, Allison is not a reference under 35 U.S.C. §102(b).

Regarding the §103 rejection, the instant generic claims have been amended to recite an adjuvant composition free of block polymer and not requiring muramyl peptides. The fact that the present invention demonstrates vaccine adjuvant activity in the **absence** of muramyl peptides is in itself an unexpected and surprising result in view of the understanding in the art of vaccine preparation prior to the instant discovery. The ability to omit muramyl peptides is a significant advantage over conventional vaccine formulations which include muramyl peptides where such formulations have

both an antigen component and an adjuvant component, both of which must be tested in clinical studies for toxicity, tolerance, efficacy etc. prior to FDA approval.

Therefore, in view of the discussion and claim amendments above, the Examiner is respectfully requested to reconsider and withdraw the current §102(b) and §103 rejections based upon the Allison disclosure.

The rejection of Claims 29-30 under 35 U.S.C. §102(b) or in the alternative under 35 U.S.C. §103 over Glass et al. (U.S. Patent 3,919,411) or Cantrell (U.S. Patent 4,803,070) is respectfully traversed.

The method disclosed by Glass et al. utilizes surfactant levels between 1 and 20% by volume. In column 6 of the patent, Glass states that the emulsion fails to form or is unsatisfactory for its intended use when the surfactant level is below 1% in the composition. In contrast, the present invention can usually be effected by having the surfactant present in a preferred amount of 0.01 to 0.5% by weight (w/w). Furthermore, Glass does not teach compositions or methods wherein the oil droplets are substantially all less than 1 micron in size. Absent the teaching of the present disclosure, it would not be obvious to decrease the oil droplet size in order to enhance the immunogenicity of the adjuvant composition taught by Glass et al.. Therefore, Glass neither anticipates or makes obvious the method of the instant invention and this ground for rejection should be withdrawn.

Cantrell teaches a method of preparing adjuvants effective as immunopotentiators for polysaccharide antigens. Cantrell's emulsion, either lipid or oil-in-water, contains the polysaccharide antigen and a biological adjuvant in a particulate form. However, Cantrell neither recognizes nor discloses the use of advantageous oil particle size. In fact, it does not appear that any of the methods used by Cantrell would result in particles of the requisite size. In columns 3 and 4, Cantrell describes various methods of blending the liquid emulsion in a vortex machine, motor-driven pestle or

blender until a milky white emulsion is obtained. This is not the same as Applicant's invention which recognizes and enables preparation of submicron oil droplets as immunopotentiators in a vaccine adjuvant composition. It is clear that Cantrell did not recognize or pursue use of submicron oil particles to increase the effectiveness of the immunogenic agent. Therefore, it is unlikely that Cantrell would be useful teaching to a skilled person pursuing the present invention. Moreover, Cantrell's adjuvant additionally requires the presence of a refined detoxified bacterial endotoxin obtained from Re mutant strains of Salmonella. Such endotoxins are not required by the present invention.

Accordingly, for all of the above reasons, these rejections should be reconsidered and withdrawn.

The Examiner's rejection of Claims 1-9 and 29-30 under 35 U.S.C. §102(b) or in the alternative under 35 U.S.C. §103 over Prigal (U.S. Patent 3,678,149) is hereby traversed.

Prigal describes water-in-oil emulsions which are different from the oil-in-water compositions claimed in the present invention. Column 5 of the patent describes that the physical makeup of Prigal's emulsion consists of globules or particles of a dispersed phase surrounded by oil. In contrast, the instant case does not describe a continuous oil phase. One would not expect the water-in-oil emulsions to have the same immunologic properties as the instant claimed emulsions.

For these reasons, Prigal neither anticipates nor makes obvious the present invention and the above rejections should be withdrawn.

Obviousness Double-Patenting

Claims 1-9 and 29-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of USSN 07/357,035.

In view of the provisional nature of this rejection, Applicant traverses the issue here presented and will consider further action upon an indication by the Examiner of patentable subject matter in the instant application.

Enclosed herewith is an Information Disclosure Statement submitted pursuant to Applicant's continuing duty under 37 CFR §1.56 to bring any information which is material to the examination of the subject application to the Examiner's attention.

It is now believed that the application is considered in good and proper form for allowance and the Examiner is respectfully requested to process this application to issue.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (415) 494-7622.

Respectfully submitted,
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Date: 9/4/91

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Enclosure: Information Disclosure Statement
PTO-1449 Form
Copies of References cited on PTO-1449 Form

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